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Molecular Database Construction and Mining: A General Approach to Unconventional Pathogen Countermeasures

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The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision, unless so designated by other documentation.

12 a. DISTRIBUTION / AVAILABILITY STATEMENT

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13. ABSTRACT (Maximum 200 words)

One general approach to unconventional pathogen countermeasures is to use specific inhibitors to cripple enzymes such as proteases that are pivotal to pathogen invasions. For example, botulinum toxins can be detoxified by inhibitors targeting the zinc endopeptidase located in the light-chain region of botulinum toxins, and anthrax can be detoxified by inhibitors targeting anthrax's lethal factor which is a zinc protease. The generality of this approach rests on the fact that all pathogen invasions are enzyme-dependent. Furthermore, viral and bacterial enzymes have high substrate specificity and can therefore be inhibited by specific inhibitors without interfering with other enzymes required for normal functions. This approach has been conceptually validated by the clinical use of protease inhibitors for treating various pathogen invasions. It is, however, not suitable for military use in its present form, because typically ten years are required to develop an effective protease inhibitor. Here we propose to use the advanced supercomputing technology to shorten the drug discovery process.

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Enclosure 1

REPORT DOCUMENTATION PAGE (SF298)
(Continuation Sheet)

Project Goal:

Develop a set of scalable supercomputer hardware and software and molecular databases for rapid, in silico identification of selective enzyme inhibitors as therapeutic agents for treating diseases of military personnel and civilians.

Background:
The vision for the project is that a selective, potent, small-molecule inhibitor should be identified in silico within 24 hours once a protein drug target is defined.

The enabling technology for the project is a set of database-mining tools used in cheminformatics and bioinformatics.

The deliverables that will emerge from the research are:

1. Database-mining software: an advanced computer docking program for identification of drug interaction sites in macromolecules and drug leads from chemical databases
2. Database-mining hardware: a low-cost, scalable supercomputer specially designed for docking studies
3. Molecular database of 1,000,000 commercially available chemicals each represented with single conformation

The biothreats targeted by the project are pathogenic proteases, the zinc-containing pathogenic proteases of anthrax and botulinum neurotoxin serotype A (Botox).

Specific Tasks:

Task 1. Develop an Improved Computer Program Enabling Efficient Parallel Calculations for Database Mining.

Task 2. Develop a Low-Cost, Scalable Computer Hardware System Optimized for Database Construction and Mining.

Task 3. Develop Molecular Databases Optimized for Database Mining.

Task 4. Test the Newly Developed Databases and Computer Software and Hardware Using Anthrax and Botox as drug targets.

Body of the Report:

1. Accomplished mile stones

Developed a low-cost, 1.1 teraflops supercomputer specifically optimized for protein structure refinement by multiple molecular dynamics simulations and for in silico screening of chemical databases for countermeasures to biological and chemical weapons. The 1.1 teraflops system was world's 42nd most powerful computer in 2002 which is equivalent to all the computing resources at the Lawrence Livermore National Lab in 2001. The 1.1 teraflops system still has the highest performance-cost ratio of 2.74 (1.1 teraflops/$0.4M), as of September 14, 2004.

Developed an MPI-based virtual drug screening program (EUDOC V43) scalable over at least 800 processors with load balance

Developed a database (CHEMIX1.1.3) of 2,458,568 unique, drug-like, 3D chemical structures

Refined the 3D structure Refined the 3D structure of the zinc-bound botulinum neurotoxin serotype Aof the zinc- and substrate-bound anthrax lethal factor

Generated the 3D structure of the zinc-bound botulinum neurotoxin serotype A in complex with a peptidic substrate (released to the Protein Data Bank, PDB code: 1UEE)

Generated the 3D structure of the zinc-bound botulinum neurotoxin serotype A in complex with a nanomolar peptidic inhibitor

Developed nonpeptidic inhibitor leads of anthrax lethal factor in collaboration with Dr. Stephen H. Leppla of the PC Program

Developed the most potent, selective, nonpeptidic inhibitor lead of botulinum neurotoxin serotype A in collaboration with Dr. James J. Schmidt and Major Charles Millard of the USAMRIID

Successfully predicted the 4D structure of a SARS cysteine proteinase complexed with its peptide substrate 20 days after the release of the SARS genome by the CDC (released to the Protein Data Bank, PDB code: 1P76)

2. Include results from collaboration with other PI's within the PC program as well as other government agencies

Identified inhibitor leads of cofactor-independent phosphoglycerate mutase in collaboration with Drs. Terrance Leighton and Mark J. Jedrzejas of the PC Program

Identified the mechanism for the solubility of problem of B-DNA binders in collaboration with Dr. Richard Tanaka of the PC Program

Identified potential drug targets of a known antiviral agent in collaboration with Dr. Jeffrey C. Bottaro of the PC Program

Described in previous reports

3. Include filed and issued patents and publications

Discovery of a New Inhibitor Lead of Adenovirus Proteinase: Steps Toward Selective, Irreversible Inhibitors of Cysteine Proteinases, Yuan-Ping Pang, Kun Xu, Thomas M. Kollmeyer, Emanuele Perola, William J. McGrath, Dave T. Green, and Walter F. Mangel, FEBS Lett., 502, 93-97 (2001)

Rational Design of Alkylene-Linked Bis-Pyridiniumaldoximes as Improved Acetylcholinesterase Reactivators, Yuan-Ping Pang, Thomas M. Kollmeyer, Feng Hong, Jong-Cheol Lee, Pamela I. Hammond, Sharie P. Haugabouk, and Stephen Brimijoin, Chem. Biol. 10, 491-502 (2003)

Improved Loading and cleavage Methods for Solid-Phase Synthesis Using Chlorotrityl Resins: Synthesis and Testing of a Library of 144 Discrete Chemicals as Potential Farnesyltransferase Inhibitors, Jewn Giew Park, Kevin J. Langenwalter, Carolyn Weinbaum, Patrick J. Casey, and Yuan-Ping Pang, J. Comb. Chem. 6, 407-413 (2004)

Nonbonded Bivalence Approach to Cell-Permeable Molecules that Target Specific DNA Sequences, Yuan-Ping Pang, Bioorg. Med. Chem., 12, 3063-3068 (2004)

Three-Dimensional Model of a Substrate-Bound SARS Chymotrypsin-Like Cysteine Proteinase Predicted by Multiple Molecular Dynamics Simulations: Catalytic Efficiency Regulated by Substrate Binding. Yuan-Ping Pang, Proteins, 57, 747-757 (2004)

Lowest Level of Theory Required for Reliable Prediction of the 3D Structures of Amide-Containing Molecules Used in Virtual Screening for Drug Leads, James D. Xidos and Yuan-Ping Pang, submitted

Three-Dimensional Model of the Zinc Endopeptidase of Botulinum Neurotoxin Serotype A Complexed with a P4–P3' Substrate Fragment Predicted by Multiple Molecular Dynamics Simulation Docking. Yuan-Ping Pang, submitted

Lowest Level of Theory Required for Reliable Prediction of the 3D Structures of Amide-Containing Molecules Used in Virtual Screening for Drug Leads. James D. Xidos and Yuan-Ping Pang, submitted

EUSCAN: A Computer Program for Determination of Molecular Flexibility of Drug-Like Chemicals with Consideration of Chemical Equivalence. James D. Xidos and Yuan-Ping Pang, in preparation

US Patent Application: Novel Antiviral Drugs: Small-Molecule Inhibitors of the NP3 Serine Protease of Dengue 2 Virus, Stanley Watowich, Andrew Russo, Robert Malmstrom, and Yuan-Ping Pang

4. Wherever possible include information that is relevant to the Department of Defense and biological warfare defense.

We believe that the technology to be developed in this project should yield effective countermeasures to both biological and chemical weapons, specifically effective countermeasures to anthrax, botulinum toxin, SARS coronavirus and West Nile Virus.

Transition Activities:

Commercial product development:

Not yet

DoD/Government product development:

The technologies for developing anthrax countermeasures have been transitioned to NIH/NIAID and ARO. We have received the funding from NIH/NIAID and ARO to further the development of anthrax countermeasures.

The technologies for developing botulinum countermeasures have been transitioned to USAMRIID. We have received the funding from USAMRMC to further the development of botulinum countermeasures.

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